Is Adjuvant Radiotherapy Effective in Intermediate-risk Surgical Stage I Endometrial Cancer?

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SUMMARY

Objective: To better understand the potential risks and benefits of adjuvant radiotherapy in patients with intermediate-risk surgical stage I endometrial cancer.

Materials and Methods: A retrospective chart review identified 55 patients with endometrial carcinoma stage IA grade 3, stage IB grade 2, and stage IC grade 1, treated at Taipei Veterans General Hospital, Taipei, Taiwan, between 1980 and 2001. The median duration of follow-up was 47 months, and patient age ranged from 34 to 82 years. One patient had stage IA grade 3 cancer, 52 had stage IB grade 2, and two had stage IC grade 1. Thirty-four patients underwent surgery alone and 21 underwent surgery plus radiotherapy. We determined the outcome of adjuvant treatment with postoperative pelvic radiotherapy or surgery alone, comparing locoregional control, overall survival, and treatment-related morbidity.

Results: There was no statistically significant survival difference between the surgery-only and surgery-plus-radiation groups ($p = 0.5927$). The 5-year overall survival rates were 97% and 95%, respectively. Univariate analysis of prognostic factors showed that only hypertension influenced survival rate ($p < 0.0344$). The overall recurrence rate was 3.6% (2/55).

Conclusions: The survival rate was high and the relapse rate was low in intermediate-risk surgical stage I endometrial cancer patients. Radiotherapy may be reserved for recurrence. [*Taiwanese J Obstet Gynecol* 2004; 43(2):101–106]

Key Words: adjuvant radiotherapy, endometrial cancer stage I, intermediate risk, overall survival

Introduction

Endometrial cancer is the most common gynecologic cancer, with an annual incidence in Western countries of 15 to 20 per 100,000 [1]. In approximately 75% of patients with adenocarcinoma of the endometrium, the invasive neoplasm is confined to the uterus at diagnosis [1]. Due to the early symptoms of irregular vaginal bleeding in this predominantly postmenopausal population, the often localized nature of the disease, and the generally high survival rate, many physicians believe that adenocarcinoma of the endometrium is a relatively benign disease.

The standard treatment for patients with stage I endometrial cancer is surgery, consisting of peritoneal lavage for cytology, total abdominal hysterectomy and bilateral salpingo-oophorectomy, and dissection of pelvic and aortic nodes. During surgery, the abdominal organs, including the diaphragm, liver, omentum, and pelvic and bowel peritoneal surfaces, should be carefully inspected and palpated. The pathologic information obtained provides an optimal basis for decisions about and design of adjuvant therapy. The most significant prognostic factors are tumor stage, histologic grade,

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and depth of myometrial invasion. Others are age, histologic type, peritoneal cytology, vascular space invasion, progesterone receptor activity, menopausal stage, and uterine size. If risk factors are present, pelvic radiotherapy (RT) is usually indicated to reduce the risk of vaginal and pelvic relapse. However, the value of postoperative RT in the treatment of patients with stage I endometrial carcinoma is controversial due to a lack of data from randomized studies and the low relapse rate. Many retrospective analyses suggest a reduction in the risk of locoregional relapse and an increase in disease-free and overall survival rates after RT [1]. Several authors report that results obtained with postoperative external beam RT (EBRT) followed by brachytherapy were similar to those using EBRT alone, with an increased rate of complications after the combination [2–4].

Two randomized studies have been reported [1,5]. In one, 540 women with endometrial stage I cancer who had received postoperative vaginal RT were randomly assigned to additional pelvic RT or observation [5], while in the other, 715 women were randomized to pelvic RT or no further treatment [1]. In the first study, although pelvic RT reduced vaginal and pelvic recurrence (2% vs 7%), more distant metastases were found in the pelvic RT group (10% vs 5%), and 5-year survival was not improved (89% vs 91%). Only the subgroup with grade 3 tumors with deep (≥ 50%) invasion showed both improved local control and survival after additional pelvic RT. In the second study, 5-year actuarial locoregional recurrence rates were 4% in the RT group and 14% in the control group ($p < 0.001$). Actuarial 5-year overall survival rates were similar in the two groups (81% vs 85%; $p = 0.31$). There were treatment-related complications in 25% of the RT group and 6% of the control group ($p < 0.0001$). Survival after relapse was significantly better for patients in the control group ($p = 0.02$). Multivariate analysis showed that for locoregional recurrence, RT and age below 60 years were significant favorable prognostic factors.

The National Comprehensive Cancer Network (NCCN) Practice Guidelines for Endometrial Cancer version 2000 recommended observation, vaginal brachytherapy (VBT), or pelvic RT with or without VBT as adjuvant therapy for patients with stage IA grade 3, stage IB grade 2, and stage IC grade 1 cancer [6]. For patients with low-grade and superficially invasive disease, VBT only was recommended, while for those with high-grade disease and deeper myometrial infiltration, treatment was vaginal RT and EBRT. However, the NCCN Practice Guidelines version 2003 recommend that adjuvant treatment for patients with stage IA grade 3, stage IB grade 2, and stage IC grade 1 should be determined by the presence or absence of adverse risk factors [6]. Adverse risk factors include advanced age, lymphovascular invasion, tumor size, depth of invasion, and involvement of the outer third of the uterus. If adverse risk factors are not present, adjuvant treatment should be observation only or VBT. If adverse risk factors are present, adjuvant treatment should include pelvic RT and/or VBT.

To better understand the potential risks and benefits of adjuvant treatment for patients with intermediate-risk stage IA grade 3, stage IB grade 2, and stage IC grade 1 carcinoma, a retrospective review of all patients treated for such endometrial cancers between 1980 and 2001 was undertaken. The outcome of adjuvant treatment with postoperative pelvic RT or surgery alone was determined by comparing locoregional control, overall survival, and treatment-related morbidity.

Materials and Methods

Between January 1980 and December 2001, 72 patients with endometrial carcinoma meeting the study criteria were treated at Veterans General Hospital–Taipei. Retrospective review of patients' charts gave the required parameters. Patients with insufficient documentation, inadequate surgery, or with miscellaneous clinical factors that did not meet the study criteria were excluded from the study. Finally, a total of 55 patients were eligible for data analysis. Patients were excluded if they had a history of double primary cancer or postoperative adjuvant chemotherapy only.

Pathologic slides were reviewed by a senior pathologist who recorded in detail all pathologic parameters, including histologic subtype, cellular grade, tumor size, and evidence of lymph vascular space invasion. All patients were staged based on the 1988 International Federation of Gynecology and Obstetrics (FIGO) system [7].

Eligible patients were divided into two groups based on the adjuvant treatment: the surgery-only and surgery-plus-RT groups. The type of RT included VBT alone, VBT plus pelvic EBRT, and pelvic EBRT alone, chosen by the attending physician. The VBT dose was 20 Gy at 500 rads/week, and the pelvic EBRT dose ranged from 45 to 50 Gy at 200 rads/day. RT morbidity was defined according to the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) scoring scheme [8].

Survival and locoregional control rates were compared between the two groups with respect to prognostic factors including age, depth of myometrial invasion, cellular grade, tumor size, and concomitant medical disease (diabetes mellitus or hypertension). Addi-

tionally, the morbidity of each treatment modality was analyzed.

Statistical methods

The Chi-squared test (with Yate's correction for 2 × 2 contingency table) or Fisher's exact test were used in univariate analysis of differences between patient groups. Survival curves were created using the Kaplan-Meier product-limit estimates method and compared using the log-rank test. A p value of less than 0.05 was considered statistically significant.

Results

Of the 55 patients with intermediate risk factors, one had stage IA grade 3 disease, 52 had stage IB grade 2, and two had stage IC grade 1. The median follow-up time was 47 months (range, 1–171 months). The patients' ages ranged from 34 to 82 years (median, 56 years). All surgical specimens were histologically proven to be endometrioid adenocarcinoma. There were 34 patients in the surgery-only group and 21 in the surgery-plus-RT group. The study groups were well balanced for age, histologic grade, and myometrial invasion (Table 1). In the surgery-plus-RT group, 11 patients received VBT, four received EBRT, and six received both VBT and EBRT. VBT consisted of high-dose-rate^{192} Ir to the vaginal vault with insertions using a cylindrical applicator. The reference point for dose prescription was 0.5 cm from the surface of the applicators, and total VBT doses ranged from 12 to 21 Gy. The EBRT technique consisted of an anterior and posterior parallel pair in three patients, and a four-field box technique in seven patients.

Among the 21 patients receiving adjuvant RT, 12 had RT-related morbidity. Thus, the incidence of mild (grade 1 or 2) late RT-related morbidity was 57%. The symptoms of late RT-related morbidity included diarrhea, abdominal cramps, constipation, rectal bleeding, dysuria, stress urinary incontinence (SUI), vaginal dryness, and vulva itching (Table 2). SUI and vaginal dryness were the most common symptoms (8 patients, 67%) in grade 1 RT-related morbidity.

There was no statistically significant survival difference between the surgery-only and surgery-plus-RT groups (p = 0.5927) (Figure 1). The 5-year overall survival rates were 97% and 95%, respectively. The 10-year overall survival rate was the same, 96%. Univariate analysis of prognostic factors showed that only hypertension had a significant influence on overall survival (p < 0.0344) (Figure 2). The 5-year overall survival rate was 98% in patients without hypertension and 93% in those with hypertension.

The overall recurrence rate was 3.6% (2/55), and both these patients had recurrence within the first 2 years. One had local vaginal recurrence and the other had left external iliac lymph node recurrence and lung metastasis. The first patient initially received adjuvant

Table 1. Patient characteristics

	Surgery only (n = 34) n (%)	Surgery + RT (n = 21) n (%)
Age		
< 60 yr	21 (62)	15 (71)
≥ 60 yr	13 (38)	6 (29)
Parity		
Nulliparous	4 (12)	1 (5)
Multiparous	30 (88)	20 (95)
Diabetes mellitus		
Yes	7 (21)	5 (24)
No	27 (79)	16 (76)
Hypertension		
Yes	12 (35)	3 (14)
No	22 (65)	18 (86)
Obesity		
Yes	13 (38)	7 (33)
No	21 (62)	14 (67)
Stage		
IA grade 3	1 (3)	0 (0)
IB grade 2	33 (97)	19 (90)
IC grade 1	0 (0)	2 (10)
Histology		
Favorable	34 (100)	21 (100)
Unfavorable	0 (0)	0 (0)
Tumor size		
< 2 cm	25 (74)	17 (81)
≥ 2 cm	9 (26)	4 (19)
LVSI		
Yes	0 (0)	1 (5)
No	34 (100)	20 (95)

RT = radiotherapy; LVSI = left ventricular systolic index.

Table 2. Morbidity of radiation

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Abdominal cramp	2
Constipation	3
Diarrhea	3
Dysuria/SUI	4
Rectal bleeding	1
Vaginal dryness	4
Vulva itching	3

SUI = stress urinary incontinence.

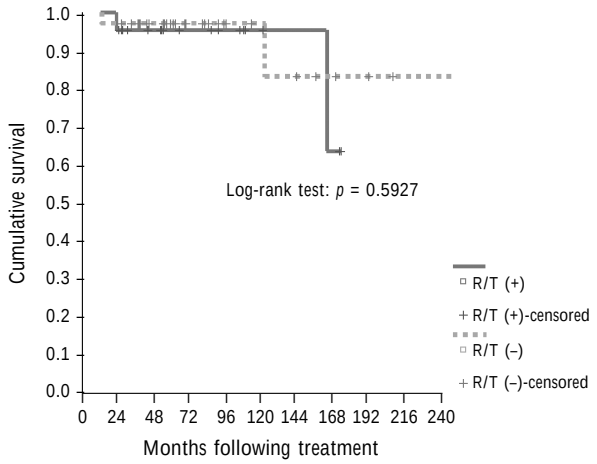

Figure 1. Survival rates of patients with endometrial cancer after staging surgery only and with adjuvant radiotherapy (p = 0.52927).

VBT only. Vaginal recurrence was proven by colposcopic biopsy 2 years later, when she received pelvic EBRT and VBT. She was alive without recurrence for 4 years after salvage treatment. The other patient initially received EBRT after staging surgery, then three courses of chemotherapy with PEC (cisplatin, epirubicin and cyclophosphamide) due to lymph node recurrence and lung metastasis 2 years later. This patient died within the same year. In the intermediate-risk group, the pelvic control rate in patients treated with surgery alone was 100%, compared with 95.23% in patients treated with surgery plus RT.

Discussion

The increasing incidence of endometrial carcinoma in the West has led to much renewed interest in the study and treatment of this disease over the last two decades. The pattern of spread and relapse of the disease, prognostic factors, relative effectiveness of adjuvant treatment, and optimization of RT techniques are still not fully understood. Many large series, such as that reported by the Gynecological Oncology Group (GOG) [9] and others [10,11], have identified major prognostic factors for survival and local failure: age, histologic

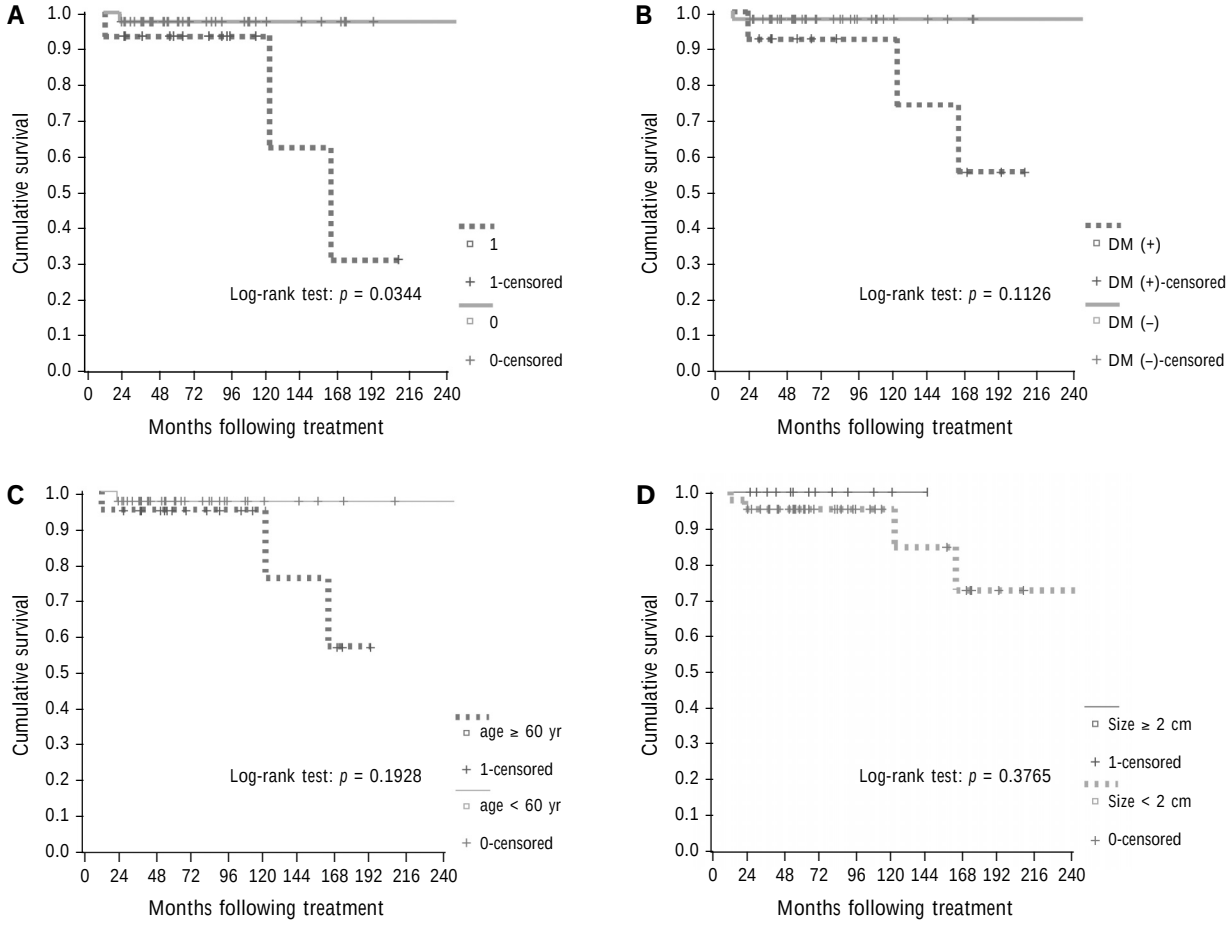

Figure 2. (A) Overall survival rates and hypertension. (B) Overall survival rates and diabetes mellitus (DM). (C) Overall survival rates and age. (D) Overall survival rates and tumor size.

grade, depth of myometrial invasion, adnexal spread, vascular space invasion, cervix/isthmus involvement, positive peritoneal cytology, and gross peritoneal disease [12]. Classically, the factors that are most often cited as prognostic of outcome in patients with endometrial carcinoma include depth of myometrial penetration and histologic grade. However, the survival rate of early stage endometrial carcinoma is generally high with surgery alone and surgery plus RT. By administering brachytherapy after hysterectomy, Eltabbakh et al obtained a 97% 15-year survival rate [13]. Ackerman et al [14] and Ayhan et al [15] reported 100% and 97% 5-year survival, respectively, using brachytherapy after staging lymphadenectomy.

In our study, there was no statistically significant difference in 5-year survival between the surgery-only and surgery-plus-RT groups (97% vs 95%; $p = 0.5927$). The use and type of adjuvant RT (VBT, pelvic EBRT, or both) for intermediate-risk stage I endometrial carcinoma remains controversial. Two well-designed prospective randomized trials questioned the use of pelvic RT. In GOG study 99, there was a difference in disease-free survival at 2 years favoring pelvic RT, but no overall survival advantage was found [16]. In the study by Creutzberg et al [17], although pelvic RT achieved significantly better locoregional control ($p < 0.001$), there was no overall survival benefit ($p = 0.31$).

The mode of adjuvant RT that should be given has also been an issue of debate; both EBRT and VBT have been used alone or in combination. Some investigators have come out in favor of EBRT [18], while others favor VBT [13], and still others endorse combined EBRT and VBT.

In the Ayhan et al study ($n = 196$, stage I endometrial carcinoma), the overall recurrence rate was 2.6% (5/196), 80% of which occurred within the first 2 years [15]. In the high-risk group (stage IC or grade 3 tumors), the pelvic control rate in patients treated with surgery plus RT was 100%, compared with 92% in patients treated with surgery alone [15]. In our study, the recurrence rate was 3.6%, all in the first 2 years. The pelvic control rate in the surgery-only group was 100%, compared with 95.23% in the surgery-plus-RT group. These results do not show the significantly better locoregional control achieved with pelvic RT in a previous prospective randomized study. This was partly because of the small sample size and partly because many cases were excluded from our study. We need longer-term observation and follow-up to validate our results.

The most common symptoms of late RT-related morbidity were SUI and vaginal dryness. As our study and many previous studies all report similar results of no significant overall survival advantage with adjuvant RT, adjuvant RT in addition to complete staging surgery is not recommended in intermediate-risk endometrial cancer.

According to the newly updated algorithms of NCCN version 2003, adjuvant treatment of patients with endometrial cancer stage IA, IB, and IC should be determined by the presence or absence of adverse risk factors. We analyzed our data to find which prognostic factors influenced outcome in patients with intermediate-risk endometrial cancer. Age (< 60 years, ≥ 60 years), tumor size (< 2 cm, ≥ 2 cm), parity (nulliparous or multiparous), lymphovascular invasion, diabetes mellitus, obesity, and adjuvant RT had no effect. Only hypertension had statistical influence on the overall survival rate ($p < 0.0344$). Due to the generally high survival rate and low relapse rate in intermittent-risk endometrial cancer, many physicians believe that endometrial cancer is a relatively benign disease and requires lower-morbidity treatment. RT may be reserved for recurrence.

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